



Numerical simulation of the effect of inhalation parameters, gender, age and disease severity on the lung deposition of dry powder aerosol drugs emitted by Turbuhaler®, Breezhaler® and Genuair® in COPD patients

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ABSTRACT

The effect of breathing parameters on the airway deposition of the inhaled aerosols with known size was intensively studied in the literature. However, in the case of dry powder aerosol drugs both the quantity and quality of the particles emitted by the inhaler and inhaled by the patients is a complex function of the patient's breathing parameters, which in turn depend also on the disease severity and current status of the patient. The aim of this study was to evaluate the impact of breathing parameters, gender, age, symptoms and exacerbation history related disease severity (GOLD groups) of chronic obstructive pulmonary disease (COPD) patients on the lung dose of four different drugs emitted by three DPIs (dry powder inhalers). Breathing profiles of 47 COPD patients were recorded while they inhaled through Turbuhaler®, Breezhaler® and Genuair® inhalers. Patient specific emitted doses and particle size distributions were determined for Symbicort® Turbuhaler®, Onbrez® Breezhaler®, Seebri® Breezhaler® and Bretaris® Genuair® aerosol drugs. Airway deposition was quantified by a validated whole respiratory tract particle deposition model. Correlation analysis of the lung doses with breathing parameters through the devices and with standard spirometric parameters was performed. The effects of gender, age and degree of disease severity (GOLD groups) on the lung doses were also studied by statistical analysis. Mean values and distributions of the deposited lung doses proved to be both drug and device specific, yielding 24.2 (± 7.8), 22.6 (± 3.6), 34.2 (± 4.8) and 23.9 (± 5.4) % values for Symbicort®, Onbrez®, Seebri® and Bretaris®, respectively. Drugs with flow rate sensitive emitted dose and emitted particle size distribution exhibited higher intersubject variability of the lung doses. The degree of correlation of lung doses with breathing parameters through the devices was also drug specific. Correlation with flow rate was the strongest for Symbicort® Turbuhaler®. Longer breath-hold increased the lung dose of all the studied drugs. Correlations of lung dose with standard spirometric parameters was generally weaker than its correlation with the parameters measured when inhaling through the devices. Men had higher lung deposition than women, younger patients had higher deposition than older ones and patients with less severe disease higher doses than those with more severe COPD, but the differences were statistically significant only upon gender and only in case of Symbicort® and Seebri®. Patients with better inhalation parameters are likely to have higher lung deposition when inhaling a drug with emitted dose and particle size distribution sensitive to the inhalation flow rate. At the same time, patients with lower lung capacity show better deposition results when inhaling from inhalers emitting a more constant amount of drug and particles with more stable aerodynamic characteristics. A more powerful inhalation significantly increases the lung dose for the drug emitted by Turbuhaler®, while long breath-hold is likely to yield significantly higher deposition for drugs emitted by Breezhaler® and Genuair®. Lung doses of two different drugs dispensed in the same inhaler can be significantly different.

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1. Introduction

Airway deposition of dry powder inhalation drugs is a result of a complex patient-inhaler-particle interaction. Breathing capabilities of the patient influence the amount of active ingredient emitted by a DPI and also its size distribution (Bagherisadeghi et al., 2017; Chapman et al., 2011; Chrystyn and Niederlaender, 2012). By the same token, the internal geometry and flow resistance of the device affect the inhalation flow rate through the inhaler, the flow structure inside the device and the number of particle-wall collisions determining the degree of disaggregation and detachment of the drug particles from their carriers (Cui and Sommerfeld, 2019; Donovan et al., 2012). Once inhaled, the airway transport and deposition of the drug depend on the drug particle characteristics, airflow parameters and airway geometry (Hofmann, 2011). Due to the large and continuously increasing number of DPI device - active ingredient combinations and the inherent inter-subject variance of the relevant spirometric parameters (Crapo and Jensen, 2003), it is a real challenge to find the most appropriate device and drug for each patient ensuring an effective airway deposition. One of the solutions that may help the choice of an appropriate device and drug would be to predict their airway deposition. A sufficiently high lung deposition is needed to reach the targeted receptors of the drugs. It should be recognized however that inhaler choice is a multifactorial decision, and the device that theoretically provides optimal deposition for a given patient may not be appropriate for some other reason (e.g. the patient cannot learn its adequate usage). Nevertheless, the availability of the predicted deposition values would help the medical professionals in a more knowledge based device choice.

Aerosol particles deposit in the airways mostly due to three mechanisms, namely inertial impaction, gravitational settling and thermal diffusion (Balásházy et al., 1990). While for the size range of current aerosol drugs deposition by Brownian (thermal) motion can be neglected, impaction and sedimentation are strongly influenced by particle size (or size distribution, in case of polydisperse systems). However, breathing parameters play also a major role in the emission and deposition of particles. In the case of DPI drugs they influence the quantity and the aerodynamic properties of the drug particles and also their fate after the inhalation. The relationship between the main inhalation parameters and the fraction of particles depositing in different regions of the airways is complicated even for the case when the size of the particles does not depend on the breathing parameters (e.g. pMDI drugs), and becomes more complex when it comes to DPI drugs (Weers and Clark, 2017). In addition, different breathing parameters have varying influence on the deposition. For instance, deposition by impaction is more influenced by the magnitude of flow rate, and deposition by sedimentation is influenced by the time available for deposition. Moreover, the relative importance of the different breathing parameters is inhaler and drug specific. Therefore, it is important to establish the dependence of all the relevant breathing parameters in case of multiple device-drug pairs. This may help in the selection of the appropriate device for every patient. In addition, if the patient cannot perform the whole breathing manoeuvre correctly, it would be useful to advise her/him on which elements of the manoeuvre concentrate more to obtain higher lung deposition.

Present work proposes to use realistic breathing data recorded on COPD patients with different degrees of disease severity while they inhaled through commonly used DPI devices and simulate their airway deposition distribution. The aim of this study is contribute to the knowledge on the personalized therapy by using the patient-specific deposition values to evaluate the relative importance of all the relevant breathing parameters in drug deposition and to find correlations between gender, age and disease groups and the lung deposition of the aerosol drugs.

2. Methods

In this work the analysis of the effect of different breathing parameters on the deposition distribution of the studied drugs was completed by identifying the key breathing parameters, simulating the aerosol deposition distributions and performing statistical analyses. The determination of the amount of drug depositing in different anatomical regions of the human airways was based on the measurement of individual inhalation profiles of COPD patients, computation of patient-specific emitted drug doses and particle size distributions and tracking of the inhaled drug particles until they deposited or left the airways by exhalation by the use of a validated deposition model. In the followings these steps will be described in more details.

2.1. Measurement of the inhalation profiles of COPD patients

Standard spirometric measurements were performed on 47 adult volunteer COPD patients (19 females and 28 males). Inhalation profiles of the same subjects were also acquired while they inhaled through Turbuhaler®, Breezhaler® and Genuair® DPI inhalers (ethical approval nr. 76-1-20/2017). For this purpose, a hand-held spirometer (Otthon Idegen™ mobile spirometer of Thor Laboratories) has been used. The spirometer was inserted between the inhaler and the mouth of the patients as shown in Fig. 1. The inhalers were realistic but emptied, thus no active substance was inhaled by the patients during the experiments. In case of Breezhaler® an empty capsule was used. Emptying the devices did not significantly affect their internal flow resistance. In addition to the registration of breathing profiles, the breath-hold time after the inhalation was also measured for each patient. The participating patients were volunteers; their written consent was obtained. The participants were instructed on the use of each inhaler by the same person according to the official patient information leaflets. The patients were previously categorized into GOLD (Global Initiative for Chronic Obstructive Lung Disease) groups (GOLD, 2019). A number of 26 patients were classified into GOLD B, 7 patients into GOLD C and 14 patients into the GOLD D group.

2.2. Selected inhalation parameters through the devices

The individual breathing profiles acquired while the patients inhaled through DPI devices are characterized by several breathing parameters. The first step of studying the relative importance of different breathing parameters in airway deposition of aerosol drugs was the identification of the relevant inhalation parameters. Inhalation flow rate is a key quantity regarding the emission of the drug from a DPI (Chrystyn et al., 2015) but also regarding its deposition within the airways (Weers and Clark, 2017). The flow rate is not constant during

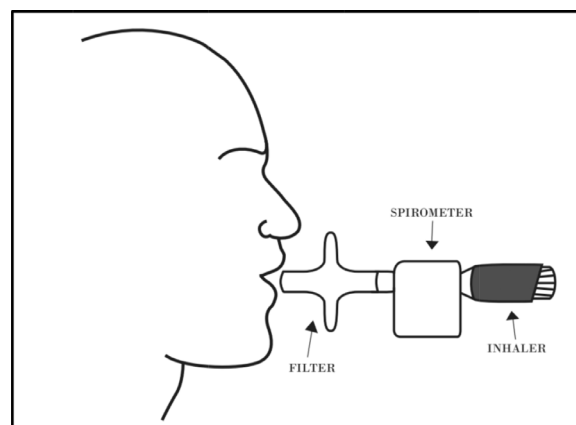


Fig. 1. Experimental setup of the inhalation profile measurements of COPD patients while inhaling through the selected inhalers.

drug inhalation, but it is time dependant. Historically, attention was paid to the maximum value of flow rate through the device (PIF_{dev}). However, mean flow rate (denoted by Q in this study) can also be a significant parameter characterizing the strength of the inhalation. It is also a useful parameter because most of the *in vitro* measurements aiming at the aerodynamic characterization of DPI drugs (impactor measurements) use constant flow rates. Due to the lack of impactor measurements using the realistic inhalation profile of each patient, mean flow rate of the patient can be used to determine the patient specific emitted doses and particles size distributions (Farkas et al., 2016). Since different sets of values of the inhaled volume (IV) and inhalation time (t_{in}) may yield the same mean flow rate, it is plausible to study the dependence of lung deposition also on these parameters (IV and t_{in}). Lung deposition depends on the inhaled air volume directly, but also indirectly through the effect of the inhaled volume on the aerodynamic characteristics of the emitted DPI drugs (Janson et al., 2017; Buttini et al., 2016). A number of authors have drawn the attention on the importance of ramp-up (acceleration) of the inspired flow (e.g. Ung and Chan, 2016; Chrystyn et al., 2015). However, the impact of flow acceleration on lung deposition could not be analysed in this study due to the lack of knowledge regarding the dose delivery performance of the studied aerosol drugs corresponding to the special flow ramp-up of each participating patient, which would require a series of *in vitro* examinations.

2.3. Calculation of the patient-specific emitted doses and particle size distributions

Currently, several drugs dispensed in Turbuhaler®, Breezhaler® and Genuair® inhalers are available, which may have different aerodynamic properties and airway deposition. In this study we selected four drugs for which sufficient data is available to consider patient specific emitted doses and particle size distributions. The four drugs were Symbicort® Turbuhaler®, Onbrez® Breezhaler®, Seebri® Breezhaler® and Bretaris® Genuair®. Symbicort® Turbuhaler® (AstraZeneca) is a drug containing anti-inflammatory inhalation corticosteroid (ICS, budesonide) and long-acting beta-agonist bronchodilator (LABA, formoterol fumarate dihydrate) active ingredients. Onbrez® Breezhaler® (Novartis) is a long-acting beta-agonist bronchodilator containing indacaterol, while Seebri® Breezhaler® (Novartis) contains glycopyrronium bromide, which is a long-acting muscarinic antagonist bronchodilator. Bretaris® Genuair® (Berlin-Chemie Menarini) is also a long-acting muscarinic antagonist bronchodilator drug containing aclidinium bromide as active substance.

Patient-specific emitted doses (ED) were determined based on the measurements available in the open literature. In the published works emitted doses are provided for different constant inhalation flow rate values. Deducing mathematical expressions of the emitted doses as functions of inhalation flow rate allowed us to assign an emitted dose to each patient based on her/his individual mean inhalation flow rate (Q). Fig. 2 demonstrates the experimentally measured emitted doses at different flow rates for the above four aerosol drugs and the power functions fitted by us. The measured emitted dose values of Symbicort® Turbuhaler® were derived from the works of de Boer et al. (2015), Bagherisadeghi et al. (2017), Chrystyn et al. (2015), Buttini et al. (2016) and Haikarainen et al. (2017). In case of Onbrez® Breezhaler® the measured dose delivered by the device was retrieved in Pavkov et al. (2010) and Chapman et al. (2011), while emission data regarding Seebri® Breezhaler® was taken from Colthorpe et al. (2013). Finally, the emission characteristics of Bretaris® Genuair® were gathered from Newman et al. (2009) and Block et al. (2010).

A similar method has been applied for the determination of patient specific size distribution of the emitted particles based on measurement results and individual inhalation flow rates. The personalized size distributions were reconstructed from the available information on the MMADs (mass median aerodynamic diameter), GSDs (geometric

standard deviation), fine particle fractions (FPF, fraction of the metered dose provided by particles with diameter $< 5 \mu m$) and aerosolized fractions (AF, defined here as the fraction of the metered dose represented by smaller particles which deposit on the impactor plates and on the filter). By the help of AF it is possible to determine the large particle fraction (LPF), which is composed of particles depositing in the impactor inlet throat and in the pre-separator, by the formula: $LPF = ED - AF$. Fig. 3 demonstrates the experimentally measured FPFs at different flow rates for the four considered drugs and the linear functions fitted to them. By the help of these functions the patient specific $< 5 \mu m$ size fraction can be determined if the inhalation flow rate of the patient is known. The measured values in Fig. 3 were derived from the published literature. The references coincided with those mentioned at the emitted doses for Onbrez® Breezhaler® and Seebri® Breezhaler® and they were complemented by the works of Johal et al. (2013), Tarsin et al. (2004), Tarsin et al. (2006), Hoppentocht et al. (2014), Corradi et al. (2014), Assi et al. (2006) and Borgström et al. (2005) in the case of Symbicort® Turbuhaler® and by the paper of Gjaltema et al. (2013) in the case of Bretaris® Genuair®.

2.4. Modelling of individual airway deposition distributions

The recorded breathing profiles and the individual-specific emitted doses and particle size distributions were used to compute the doses deposited in the extrathoracic airways and in the lungs of the patients. For this purpose, a whole respiratory tract deposition model was used. The model tracks large numbers of inhaled particles (typically 100,000) until they deposit or leave the airways by exhalation. The initial version of the aerosol particle deposition model was developed by Koblinger and Hofmann (1985). In the original model the deposition of particles in the extrathoracic airway region is estimated based on empirical formulas derived by Cheng (2003). However, Cheng's formulas and other similar relationships established based on experimental measurements (e. g. Stahlhofen et al., 1989; Rudolf et al., 1994; Heyder et al., 1986) were not designed for use with DPI's. It is a particularity of the inhalation from DPI's that the deposition in the oral cavity and throat is influenced by the high velocity jet flow exiting the inhaler. Lin et al. (2001) have demonstrated that the diameter of the mouthpiece has a significant effect on the oral deposition with lower deposition for larger nozzle diameter. DeHaan and Finlay (2004) derived oral deposition formulas accounting for the nozzle diameter and turbulence. However, their formulas can be used only if the size distribution of the particles emitted by DPI is known. In practice, in compliance with the protocols described in the Pharmacopoeias (Council of Europe, 2020; United States Pharmacopeia, 2020), aerosol drug particle size measurement is performed by impactors preceded by a 90° bent tube (throat) and sometimes a pre-separator. The total mass of particles depositing in the impactor throat is measured, but information is missing regarding their size distribution, which is determined only for the particles entering the impactor. In this study, we considered that the experimentally measured mass of drug depositing in the impactor throat would deposit also in the mouth-throat region of the patients inhaling the same drug with the same inhalation flow rate. In addition, the empirical formula of Stahlhofen et al. (1989) was applied to estimate the mass (dose) of drug depositing in the laryngeal region which is not included in the impactor measurements. Indeed, the authors of the work stated that in their experiments the oral cavity and pharyngeal deposition was negligible, thus their model yielded an estimate primarily of the laryngeal deposition. Fig. 4 demonstrates that this approach ensures a realistic estimation of the extrathoracic drug deposition. In the tracheobronchial and acinar airway regions we applied the original model of Koblinger and Hofmann (1985). In this model the fate of the inhaled particles is predicted in a stochastic lung structure with morphometric characteristics (tube lengths and diameters, branching and gravity angles) based on a database of Raabe et al. (1976). In the acinar part of the airways the particles are tracked

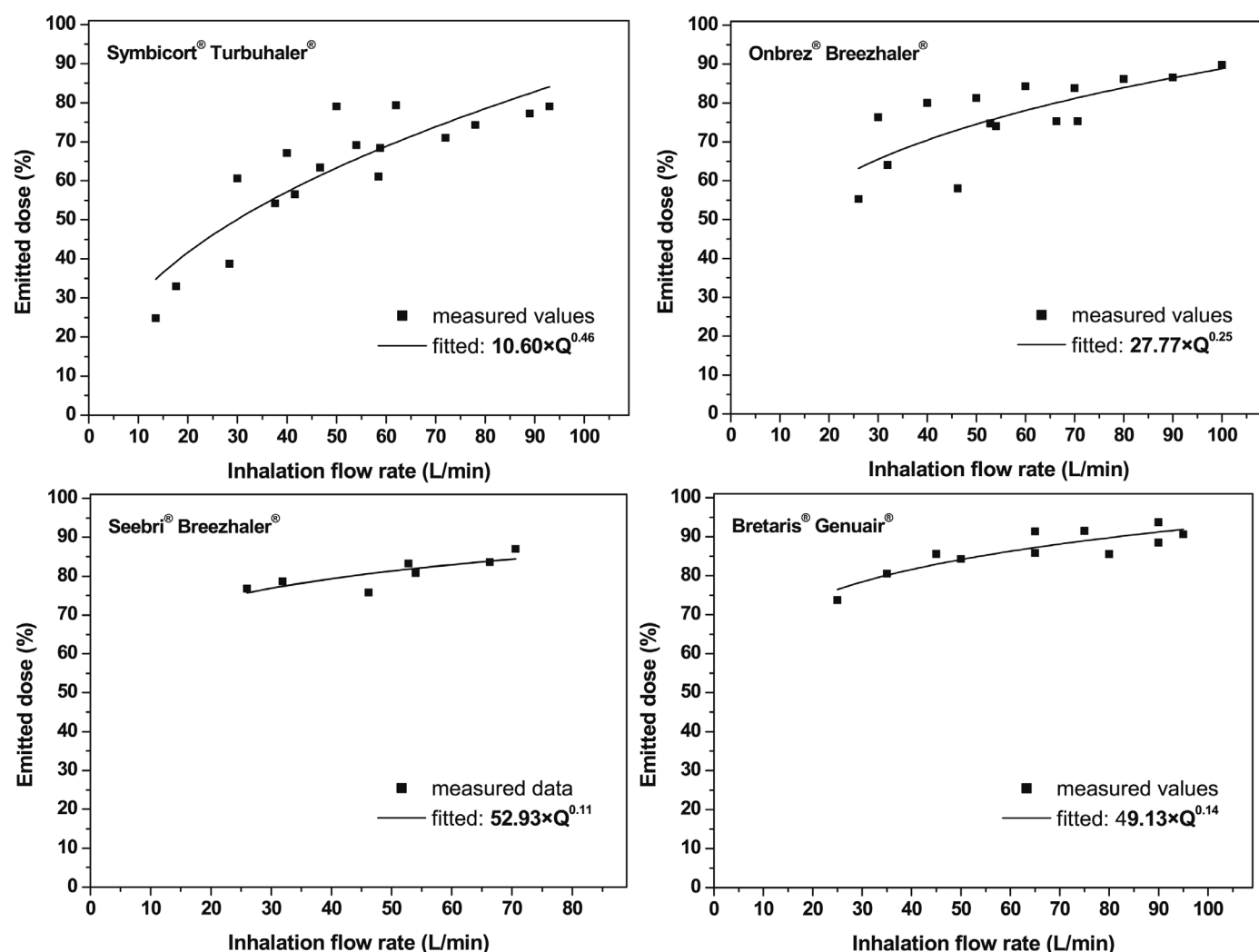


Fig. 2. Measured emitted dose values of Symbicort® Turbuhaler® (upper left), Onbrez® Breezhaler® (upper right), Seebri® Breezhaler® (lower left) and Bretaris® Genuair® (lower right) as a function of inhalation flow rate derived from the open literature and corresponding power function fits. The fitted functions were used for the determination of patient specific emitted doses (Symbicort®: $ED = 10.6 \times Q^{0.46}$, Onbrez®: $ED = 27.77 \times Q^{0.25}$, Seebri®: $ED = 52.93 \times Q^{0.11}$, Bretaris®: $ED = 49.13 \times Q^{0.14}$). All emitted doses are expressed as a percent of metered dose. ED – emitted dose, Q – inhalation flow rate.

in a geometry reconstructed from the description of Haefeli-Bleuer and Weibel (1988). The intersubject variability of the airway geometry was taken into account by the stochastic nature of the model and by individual scaling of the airways based on the available anthropometric (height) and volumetric (functional residual capacity, tidal volume) data of the patients. The changes in airway geometry due to the disease were also accounted for. The bronchial airways were contracted with different probabilities and the extent of contraction was dependant on the disease severity. The conductive part of the acinar airways could also be contracted depending on the disease severity. The dilatation of the alveoli in the acinar region was also taken into account. The probability and extent of contraction of the bronchial airways and the conductive part of the acinar airways and the probability and extent of dilatation of the alveoli in the acinar region are listed in Tables A1 – A2 of the Supplementary Material.

2.5. Model validation

The numerical model described in the previous section was validated against experimental deposition data of different types of aerosols, including therapeutic ones (Farkas et al., 2015, 2016, 2017; Farkas et al., 2018). In addition, before performing the simulations the deposition model was tested for the inhalers and active ingredients

considered in this study. This task was accomplished by comparing the results of available scintigraphic deposition measurements and numerical estimations with the corresponding simulation results obtained by our model for the same set of input breathing parameters and aerosol characteristics.

Borgström et al. (1994) have measured upper airway and lung deposition fractions of budesonide emitted by Turbuhaler® of ten (five women) healthy subjects whose FEV₁ ranged between 83 and 127% of predicted. The peak inhalation flows of the patients were between 53 and 64 L/min, inhaled volume between 2.07–4.97 L and breath-hold time after the inhalation was 10 s. Aerodynamic characteristics of the emitted particles corresponded to 60 L/min inhalation flow rate. Their size distribution was determined by a multistage liquid impinger. Chapman et al. (2011) evaluated the regional (oropharyngeal and intrathoracic) deposition of indacaterol dispensed in Breezhaler® in seven COPD patients (4 women) whose peak flow varied between 47 and 99 L/min, inhaled volume ranged between 1.0–2.2 L, inhalation time between 1.3–3.2 s and breath-hold time was 10 s. Particle size distributions were determined for the individual breathing profiles by a Next Generation Impactor. Contrary to the studies presented above, drug deposition was not measured but quantified by the help of an open source model (ICRP66 model). Colthorpe et al. (2013) assessed extra-thoracic and lung deposition fractions of glycopyrronium emitted by

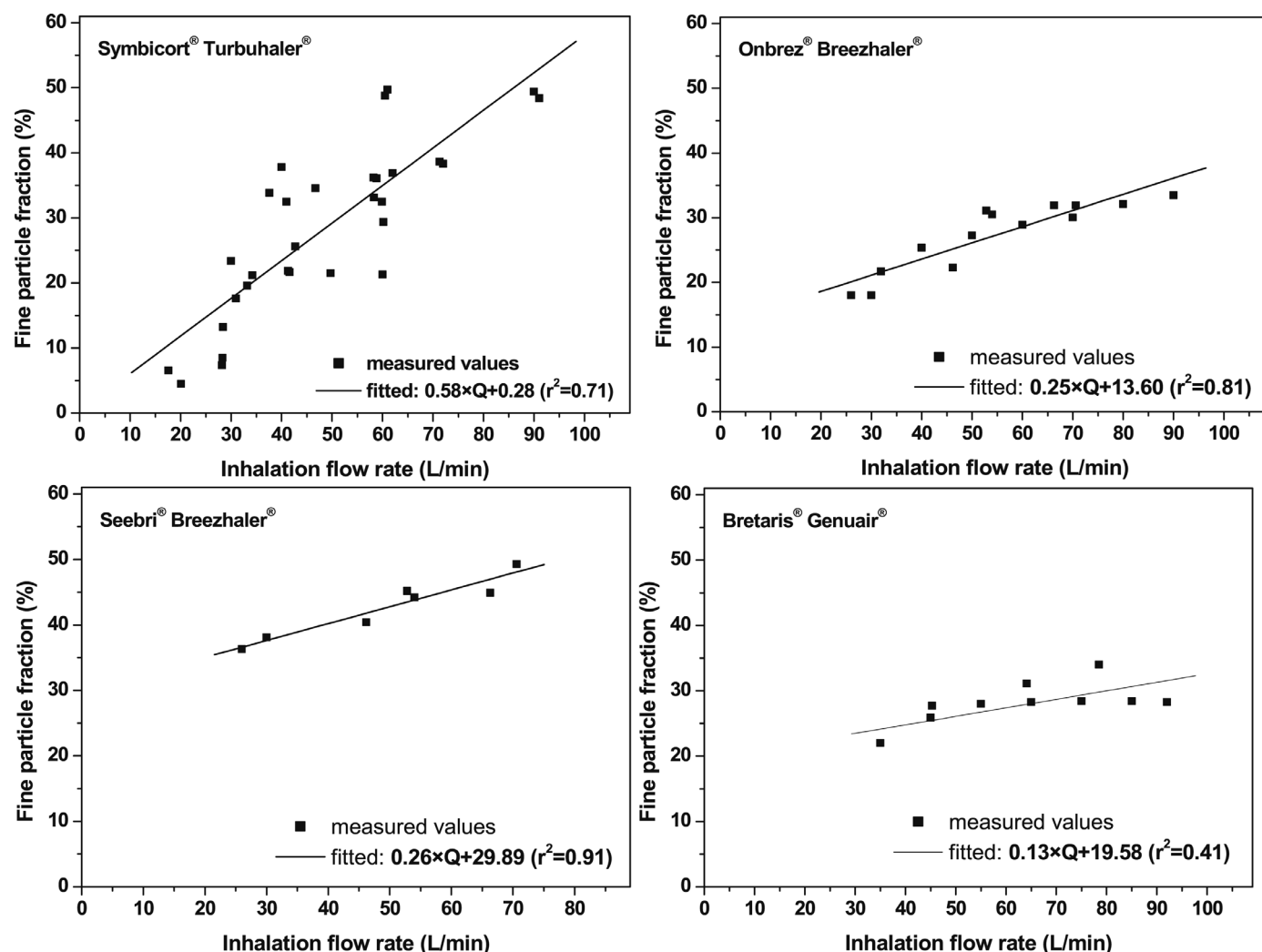


Fig. 3. Measured fine particle fraction values of Symbicort® Turbuhaler® (upper left), Onbrez® Breezhaler® (upper right), Seebri® Breezhaler® (lower left) and Bretaris® Genuair® (lower right) at different inhalation flow rates gathered from the open literature and the corresponding linear fits. The fitted functions were used for the determination of patient specific $< 5 \mu\text{m}$ size fractions (Symbicort®: $\text{FPF} = 0.58 \times Q + 0.28$, Onbrez®: $\text{FPF} = 0.25 \times Q + 13.6$, Seebri®: $\text{FPF} = 0.26 \times Q + 29.89$, Bretaris®: $\text{FPF} = 0.13 \times Q + 19.58$). FPF – fine particle fraction, Q – inhalation flow rate, r – correlation coefficient.

Breezhaler® in the same seven COPD patients who were also the subjects of the work of Chapman et al. (2011). Particle aerodynamic characteristics were determined for the individual breathing profiles by a Next Generation Impactor. Airway deposition was simulated by the ICRP66 model. Finally, Newman et al. (2009) experimentally measured extrathoracic and lung deposition fractions of the inhaled acclidinium bromide in 12 healthy male volunteers with FEV_1 between 84 and 121% of predicted. Their average peak flow through the device was $79 (\pm 9.4)$ L/min, inhaled volume $3.91 (\pm 0.72)$ L and breath-hold time was $9.7 (\pm 0.6)$. The aerodynamic particle size distribution was determined by a 5-stage multistage liquid impinger at 90 L/min airflow rate.

Fig. 4 depicts the results of the above works in comparison with the deposition values of present simulations performed for the same inputs. As the figure demonstrates, there is a good agreement in terms of regional deposited doses. The good match indicates that our computational model is appropriate for the simulation of the deposition of aerosol drugs in general, and for the prediction of regional doses of the modelled active ingredients in particular.

2.6. Statistical analysis

An analysis of the correlation of the computed lung doses with the

breathing parameters characterizing the inhalation through the selected devices (Q, t_{b-h} , IV, t_{in} , PIF_{dev}) was performed. The strength of the correlation was expressed in terms of Pearson coefficients and any correlation was considered significant when $p < 0.05$. In addition, the correlation of lung deposition with baseline spirometry breathing parameters expressing the breathing status of the patient (expiratory volume at the end of the first second of forced exhalation: FEV_1 , forced vital capacity: FVC, Tiffeneau index: FEV_1/FVC , peak inhalation flow: PIF, peak expiratory flow PEF, inspiratory vital capacity: IVC) was studied. For the sake of clarity, it is worth noting that PIF denotes the peak inhalation flow measured by standard spirometry, while PIF_{dev} is the peak inhalation flow measured while inhaling through the device ($\text{PIF}_{dev} < \text{PIF}$). By the same token, mean values of lung doses characteristic of different age, gender and GOLD groups were analysed conducting two-sample t-tests. Two age groups were formed. The cut-off age was 65 years, because most of the developed countries have accepted the chronological age of 65 years as a definition of 'elderly' or older person. Two groups were analysed also upon the classification of patients based on symptoms and exacerbation history. The first group (GOLD B) included 26 patients and the second group (GOLD C and D) 21 patients. All statistical analyses have been performed by the application of OriginPro 2018 (version b9.5.0.193, OriginLab Corporation, Northampton, Massachusetts, USA).

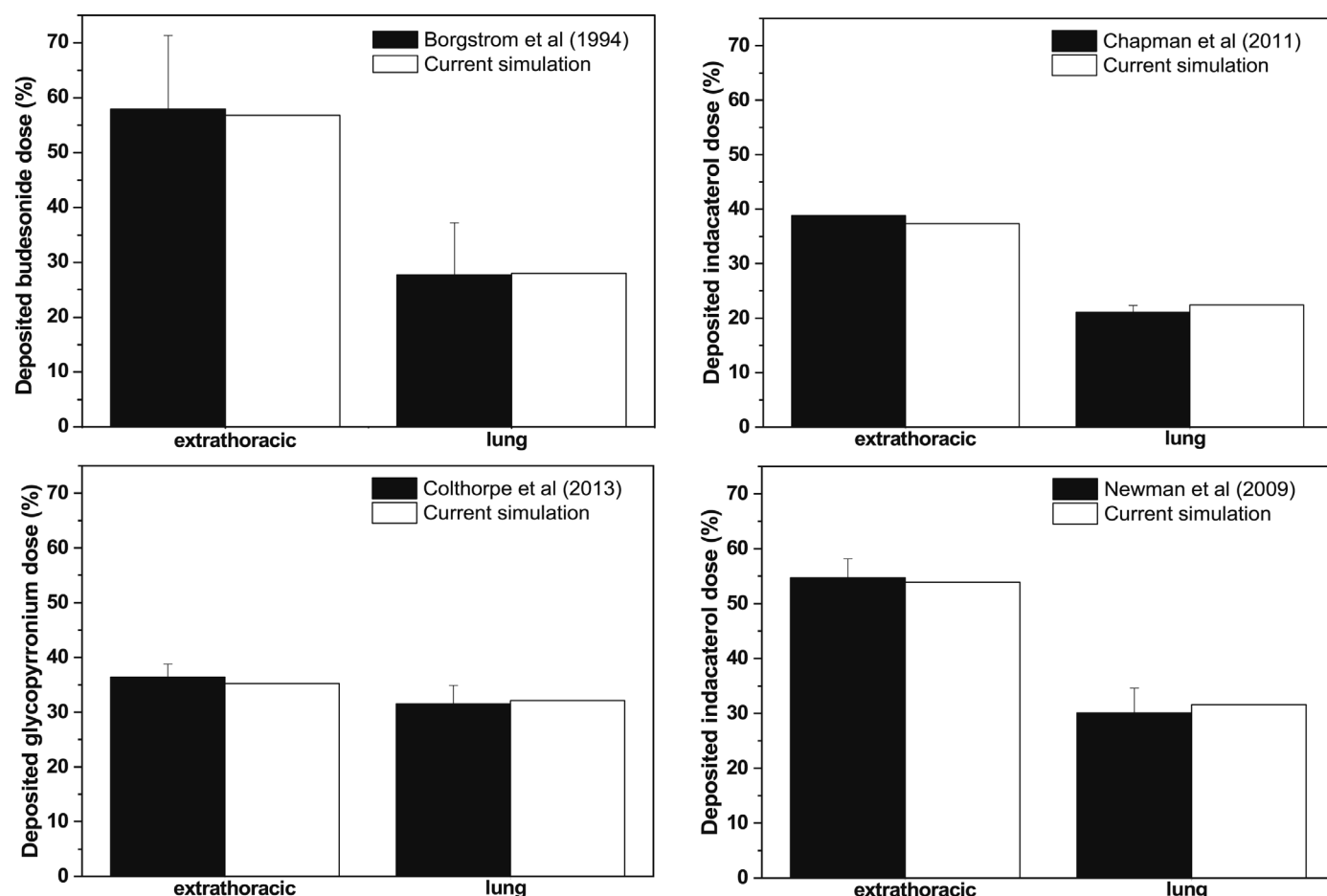


Fig. 4. Comparison of experimental deposition (filled columns) and the corresponding simulation results for budesonide (upper left), indacaterol (upper right), glycopyrronium (lower left) and aclidinium bromide (lower right) active ingredients. All deposition fractions are provided as a percent of the metered dose.

3. Results and discussion

In this section, the results of patient specific airway deposition simulations of the studied drugs will be presented. The relationships between the lung doses of the patients and their individual breathing parameters through the selected devices will be analysed. The correlations between the lung dose and baseline spirometric parameters will also be presented. Finally, the future perspectives of patient specific device-drug pair choice and optimization of drug delivery based on the predicted lung depositions will be discussed.

3.1. Distribution of individual-specific lung doses of the selected aerosol drugs

As a first step, the patient specific emitted doses and particle size distributions were calculated based on the fitted formulas deduced and presented in the methods sections (see Figs. 2 and 3). The average values and the ranges of the computed emitted doses (ED, as a percent of metered dose) and mass median aerodynamic diameters (MMAD) of the 47 patients are presented in Table 1.

The distribution of the lung doses of 47 COPD patients obtained based on the individual breathing parameter values and patient specific emitted doses and aerosol size distributions can be seen in Fig. 5. Drug doses deposited in the lungs are expressed as a percent of the metered dose. Mean values and standard deviations of the lung dose for a given drug are also demonstrated. A comparison of the deposition values in Figs. 4 and 5 reveals that lung deposition fractions of realistic patients can be lower than the values measured by scintigraphy where the volunteers are often healthy subjects. Indeed, the mean values of the

Table 1

Mean values and ranges of the computed individual specific emitted doses and mass median aerodynamic diameters of the emitted aerosols for Symbicort® Turbuhaler®, Onbrez® Breezhaler®, Seebri® Breezhaler® and Bretaris® Genuair® drugs. ED – emitted dose, MMAD – mass median aerodynamic diameter.

	ED (%)	MMAD (μm)
Symbicort® Turbuhaler®	62.5 (43.4–86.3)	2.4 (1.3–3.2)
Onbrez® Breezhaler®	77.6 (65.1–93.2)	3.0 (1.9–3.6)
Seebri® Breezhaler®	83.3 (76.5–96.6)	2.7 (2.5–2.8)
Bretaris® Genuair®	82.9 (71.0–90.2)	2.5 (2.2–2.7)

calculated lung doses in Fig. 5 agree well with the mean values of the lung deposition fractions of Onbrez® Breezhaler® and Seebri® Breezhaler® which were measured in COPD patients, but the present values are lower for Symbicort® Turbuhaler® and Bretaris® Genuair® where the volunteers of the scintigraphic studies were healthy subjects. Therefore, one of the outcomes of the present work is that scintigraphic lung deposition values of different aerosol drugs that can be retrieved in the open literature represent mostly the upper limit of lung doses, especially if the measurements were performed on healthy volunteers.

Besides the mean values of the lung dose, it is worth analysing their intersubject variability, as well. Based on Fig. 5, while for some drugs the majority of lung doses fall into a relatively narrow interval (Onbrez®, Seebri® and partly Bretaris®), for other drugs the inter-individual spread is more consistent (e.g. Symbicort® Turbuhaler®). The intersubject variability of the lung dose is strongly related to the flow rate dependence of the emitted dose and particle size distribution. It is clear from Figs. 2 and 3 that both the amount of the emitted drug and its size

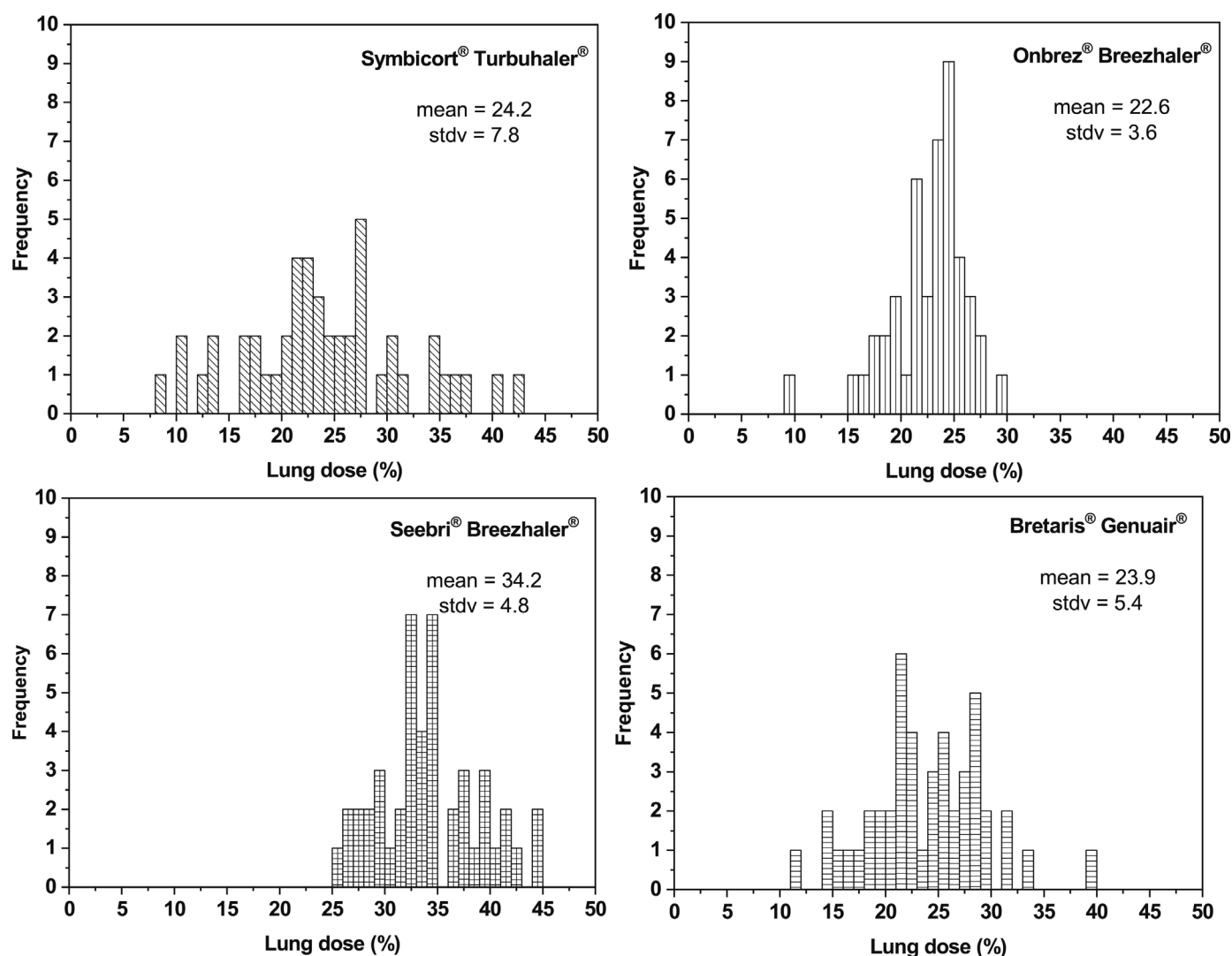


Fig. 5. Distribution of the simulated individual lung doses in case of Symbicort® Turbuhaler® (upper left), Onbrez® Breezhaler® (upper right), Seebri® Breezhaler® (lower left) and Bretaris® Genuair® (lower right) aerosol drugs. The corresponding mean extrathoracic doses were 33%, 22.6%, 36% and 51.2%, respectively.

Table 2

Minimum and maximum values of the calculated lung doses (as a percent of metered dose) and the corresponding breathing data through Turbuhaler®, Breezhaler® and Genuair® for Symbicort® Turbuhaler®, Onbrez® Breezhaler®, Seebri® Breezhaler® and Bretaris® Genuair® aerosol drugs. Q – mean inhalation flow rate through the inhaler, t_{b-h} – breath-hold time, IV – inhaled volume, t_{in} – inhalation time, PIF_{dev} – peak inhalation flow through the inhaler.

	Flow resistance ($Pa^{0.5} s L^{-1}$)	Lung dose (%)	Q (L/min)	t_{b-h} (s)	IV (L)	t_{in} (s)	PIF_{dev} (L/min)
Symbicort® Turbuhaler®	64.2	min: 8.9	17.1	3	1.2	4.3	37.2
		max: 42.4	91.1	5	3.4	2.2	216.6
Onbrez® Breezhaler®	36.2	min: 9.7	126.6	5	3.7	1.7	209.4
		max: 29.2	59.3	12	3.6	3.7	75.0
Seebri® Breezhaler®	36.2	min: 25.9	37.3	3	1.3	2.1	66.6
		max: 44.7	89.6	18	2.5	1.7	171.6
Bretaris® Genuair®	58.4	min: 18.6	17.5	3	1.2	4.3	38.4
		max: 39.8	87.3	5	3.6	2.5	181.7

distribution are the most sensitive to the variance of inhalation flow rate in case of Symbicort® Turbuhaler®. Fig. 5 demonstrates that for this drug the inter-individual variance of lung dose is also the highest. It is worth noting that Onbrez® and Seebri® provided different deposition distributions both in terms of mean values and standard deviations, though the two drugs were emitted by the same device. The fraction of the metered dose depositing in the lungs of the same COPD patients is in average 1.5 times higher for Seebri® than for Onbrez®. As the particles are emitted by the same device, the difference is probably due to

the different compositions and different formulation processes of the two drugs. It is well-known that unlike Onbrez®, Seebri® does contain MgSt, an ingredient controlling the adhesive forces between the active substance and the carrier (Jetzer et al., 2018). This may also be the reason why Seebri® has a much higher fine particle fraction (see Fig. 3). This translated in higher lung doses in case of Seebri® but also in a higher spread of the individual lung dose values. It is also worth noting that Genuair® has a built in mechanism with the role of blocking the emission of drug until the inhalation flow rate of the patient exceeds the

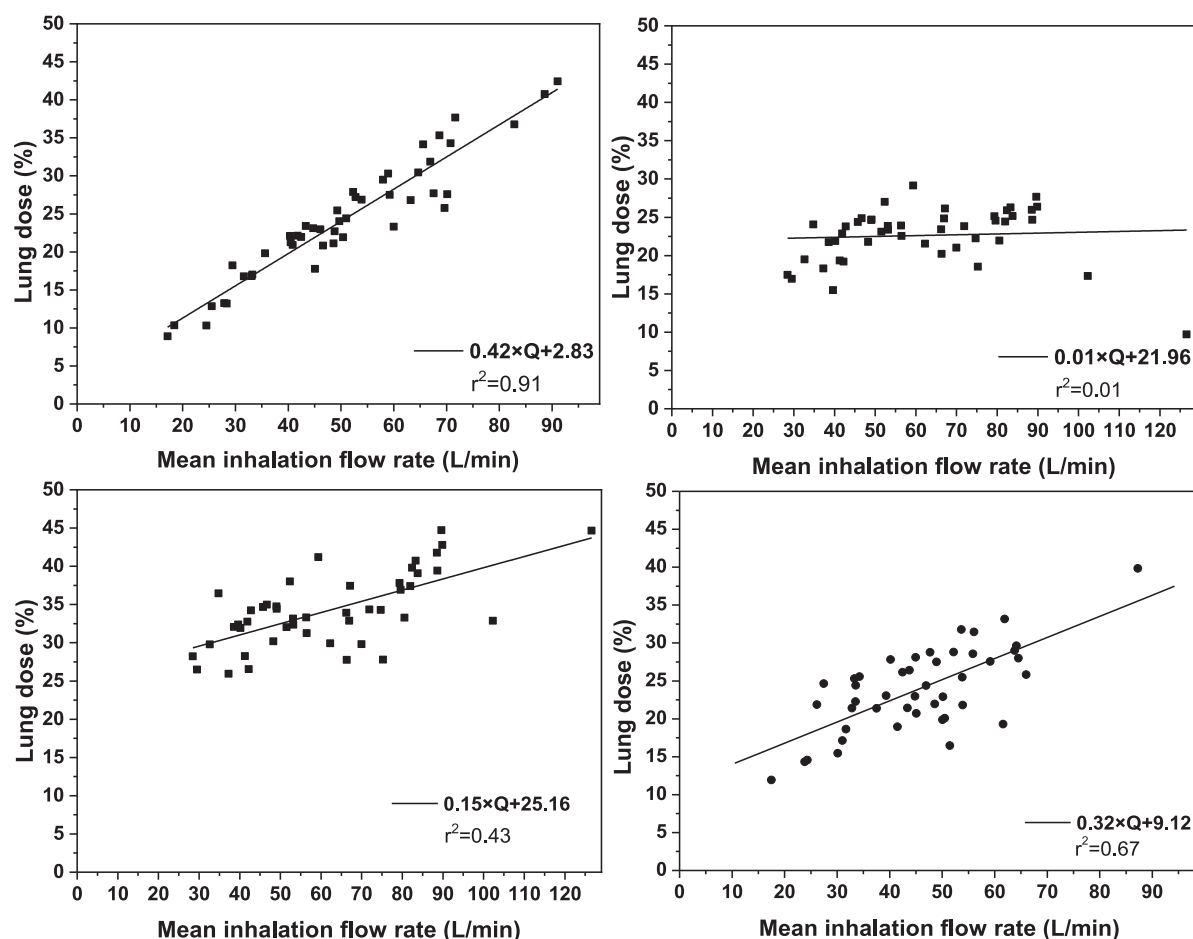


Fig. 6. Dependence of lung dose on the mean inhalation flow rate (Q) through the device in case of Symbicort® Turbuhaler® (upper left panel), Onbrez® Breezhaler® (upper right panel), Seebri® Breezhaler® (lower left panel) and Bretaris® Genuair® (lower right panel). All the lung doses are expressed as a percent of metered dose.

threshold of 40–45 L/min (Magnussen et al., 2009; Chrystyn and Niederlaender, 2012; der Palen, 2014). The aim of this mechanism is to obtain a high and relatively constant emitted dose and also to ensure that the airflow is sufficiently strong to detach the drug particles from their lactose carriers. In this study there were six patients whose PIF_{dev} was around the threshold value. Although their deposition values were included in the distribution in Fig. 5, in reality the drug may not be released for some of them. Since the lung dose values for these patients are low, the distribution of lung doses in Fig. 5 corresponding to Bretaris® Genuair® may be even narrower (starting from 18% of the metered dose). If these patients were discounted, the mean (\pm stdv) lung dose of Genuair® would be 25.2 (\pm 4.4)%. Table 2 presents the extreme values of lung doses for the four drugs and the breathing parameters corresponding to them. Airflow resistances of the DPI inhalers provided by Ciciliani et al. (2017) are also presented in the table. As the table demonstrates, the deposition of each drug could be improved consistently by optimizing the breathing. The lung doses of the patients with the highest lung deposition are 1.7 (Seebri® Breezhaler®) - 4.8 (Symbicort® Turbuhaler®) times higher than the lowest lung doses of the same drug. Another aim of the table is to reveal in what conditions the same drug yields low or high lung deposition values after identical patient instructions. Based on the data in Table 2, deposition of Symbicort® Turbuhaler® was the highest for the patient who inhaled very forcefully and the lowest for the patient who had a weak inhalation. To the contrary, Onbrez® Breezhaler® had the lowest lung deposition for a patient with very high mean inhalation flow rate which caused a high upper airway deposition by impaction of drug particles. Interestingly, the same patient had the highest lung dose of Symbicort® and the

lowest lung dose of Onbrez®. It means that the same strong inhalation of the same person led to high emitted dose and small inhaled particles with high lung deposition of Symbicort®, but to a too high flow rate through Breezhaler® (which has a much lower flow resistance) causing high throat deposition. This highlights again the importance of patient tailored drug and device choice. The highest lung dose of Onbrez® was achieved by a patient with sufficiently high (but not too high) mean inhalation flow rate, high inhaled volume and long breath-hold. Similarly, sufficiently high mean flow rate and very high breath-hold time caused the highest deposition of Seebri®. In case of Bretaris® high mean flow rate and high inhaled volume made the difference.

3.2. The influence of device and patient specific breathing parameters on the lung dose

As Fig. 5 and Table 2 suggest, the sensitivity of the lung dose to different breathing parameters is drug and inhalation device specific. However, the exact correlations can be revealed only by statistical analyses. Figs. 6–10 depict the dependence of lung dose of Symbicort® Turbuhaler®, Onbrez® Breezhaler®, Seebri® Breezhaler® and Bretaris® Genuair® on different breathing parameters characterizing the inhalation of the patients through the three devices. The values of Pearson coefficient and the nature of the correlation (significant or not) are also summarized in Table 3.

It is evident from Table 3 and Figs. 6–10 that for Symbicort® Turbuhaler® the lung dose correlates strongly with the mean flow rate (Q) and the correlation with PIF_{dev} and IV is also good and significant. However, the amount of this drug depositing in the lungs of COPD

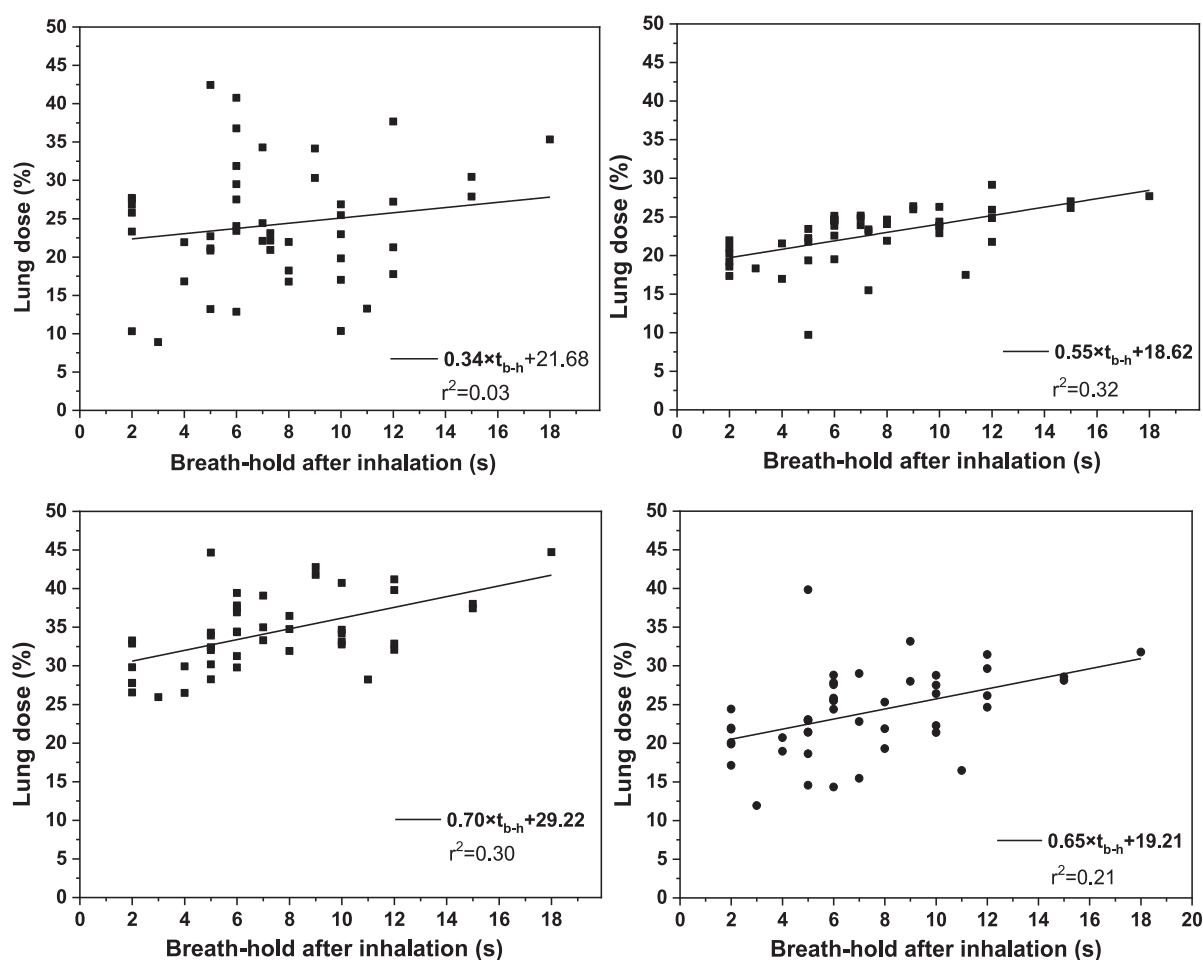


Fig. 7. Dependence of lung dose on the breath-hold time after inhalation (t_{b-h}) in case of Symbicort® Turbuhaler® (upper left panel), Onbrez® Breezhaler® (upper right panel), Seebri® Breezhaler® (lower left panel) and Bretaris® Genuair® (lower right panel). All the lung doses are expressed as a percent of metered dose.

patients does not correlate significantly with t_{in} and t_{b-h} , though longer breath-hold increases the lung dose to some extent. The good correlation with flow rate can be attributed to the strong dependency of the emitted dose and fine particle fraction on this parameter (see Figs. 2 and 3). Lung deposition of Onbrez® Breezhaler® exhibited the weakest correlation with the inhalation parameters considered, except the breath-hold time which was in moderate and significant correlation with the lung dose. In case of Seebri® Breezhaler® there was moderate or good and significant correlation with all the parameters, except for t_{in} , which did not correlate significantly with the lung dose. The different behaviour of the two drugs emitted by the same device was already discussed in the previous subsection. Finally, lung doses of Bretaris® Genuair® were in good and significant correlation with IV, Q and PIF_{dev} , in moderate and significant correlation with t_{b-h} , but no significant correlation with t_{in} . Summarizing the results in Fig. 6–10, the correlation of lung deposition with different breathing parameters through the devices is drug and device specific. The lung dose correlates strongly with flow rate (PIF_{dev} and Q) for the device-drug pairs with strong dependence of ED and FPF on the inhalation flow rate. In these cases, there is a good correlation also with IV. The increase of breath-hold time results in increased lung dose, but the increase is drug and device specific. Each drug contains a certain amount of extrafine ($< 2 \mu m$) particles. These particles penetrate into the lungs but they may be exhaled if there is not enough time for them to deposit by gravitational settling (Horváth et al., 2017). The results in Fig. 7 clearly demonstrate the need for a better education of the patients about the high importance of breath-hold after the inhalation of the drug. It is also clear from the Fig. 9 that inhalation time correlates the least with the lung

dose. In conclusion, care should be taken when advising the patients on which phase of the breathing manoeuvre concentrate more, because the sensitivity of the lung dose on these phases is drug and device dependant.

3.3. Correlations of lung dose with the baseline spirometric parameters

Figs. 6–9 demonstrate the possibilities of predicting the deposited lung doses as a function of inhalation parameters that are achieved by the COPD patients when inhaling through the devices. However, in the clinical practice these parameters are not measured routinely. Therefore, it is useful to study the dependence of the lung dose also on standard spirometric parameters. Table 4 presents the correlations between the calculated doses of the four drugs deposited in the lungs of the volunteers with FEV_1 (%), FEV_1 (L), FVC (%), FVC (L), FEV_1/FVC (%), PIF (L/min), PEF (L/min), and IVC (L). Based on this correlation table, the degree of correlation between the amount of active ingredient depositing in the lungs of the patients and baseline spirometric parameters is highly drug and device specific. For Symbicort® Turbuhaler® there was significant and weak to moderate correlation with almost all the studied parameters. The deposition of Bretaris® Genuair® correlated significantly only with FEV_1 and FVC expressed in litres and with PIF , PEF and IVC. On the other hand, Onbrez® Breezhaler® did not exhibit any significant correlation with the parameters considered except IVC, while Seebri® Breezhaler® correlated with all the baseline spirometric parameters, except FEV_1/FVC (%). An important message of these results is that while for some drugs a high lung deposition can be predicted based on normal spirometric data, for other drugs this prediction

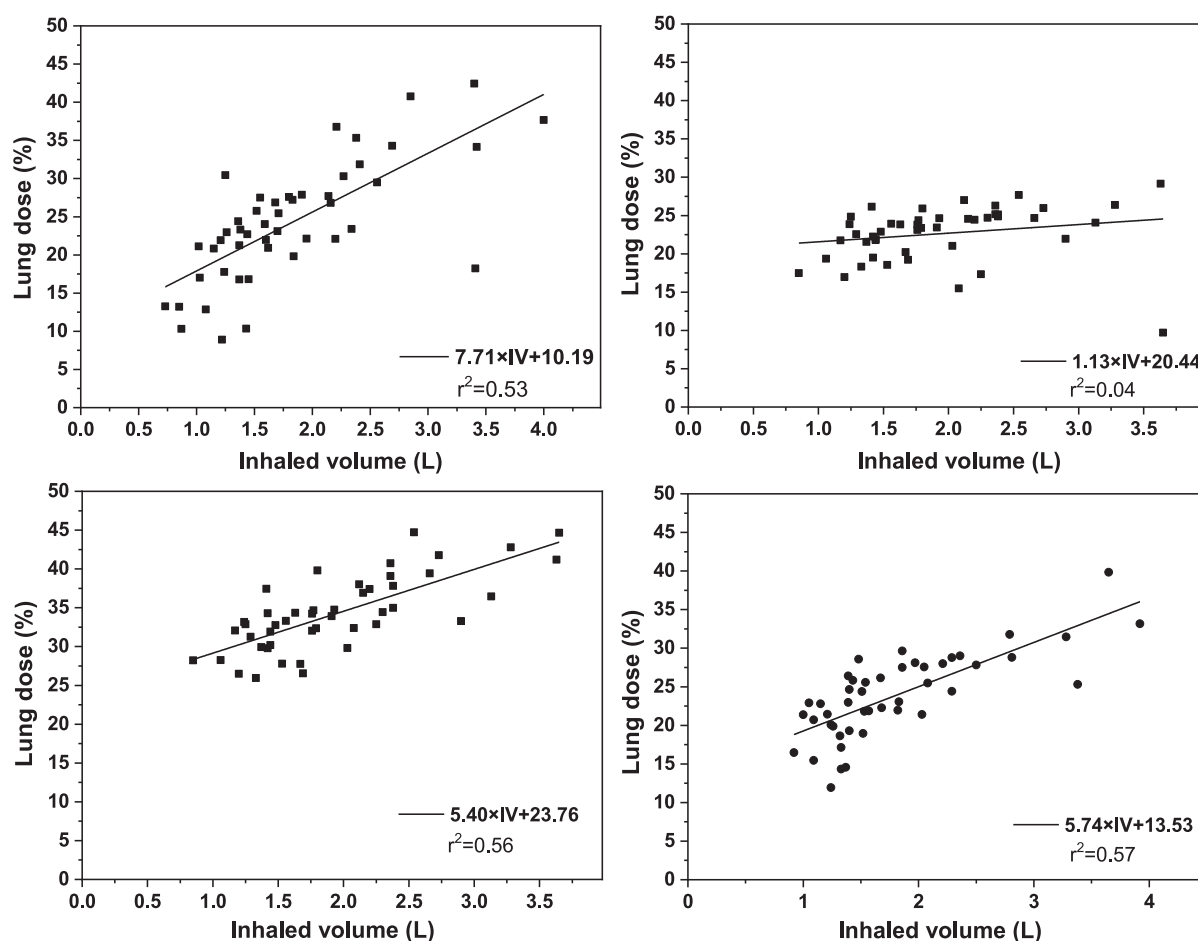


Fig. 8. Dependence of lung dose on the inhaled air volume (IV), in case of Symbicort® Turbuhaler® (upper left panel), Onbrez® Breezhaler® (upper right panel), Seebri® Breezhaler® (lower left panel) and Bretaris® Genuair® (lower right panel). All the lung doses are expressed as a percent of metered dose.

is uncertain (without numerical simulations). Another observation is that lung deposition generally correlated better with inhalation parameters (PIF, IVC) than with expiratory parameters (FEV₁, FVC) with the exception of PEF. Since deposition of drugs is a result of an inhalation manoeuvre this result seems to be logical. Therefore, it proves to be incorrect to predict the success of drug inhalation based on these expiratory parameters. In this context, especially FEV₁ (%) is thought to be a good indicator by many specialists. However, present results demonstrate that the correlation of lung dose with this parameter is one of the weakest. It was also shown in one of our previous studies that for the same patients and for the same three devices no significant correlation existed between PIF_{dev} and FEV₁ (%), though FEV₁ (%) correlated significantly with the native PIF (Farkas et al., 2019).

3.4. Effect of gender, age and disease group

The results of two-sample t-tests carried out to study the effect of gender on the lung deposition of COPD patients are summarized in Table 5. The tests revealed that lung doses were consistently higher for men than for women and the spread of values was also higher in men. The highest difference between the mean lung dose values characteristic of women and men was observed for Symbicort® Turbuhaler®, then Seebri® Breezhaler® and Bretaris® Genuair®, while for Onbrez® Breezhaler® the difference was only minor. Significance level ($p = 0.05$) was reached for Symbicort® Turbuhaler® and Seebri® Breezhaler®. It seems that for drugs with high influence of airflow rate and inhaled volume on the amount and size of the emitted particles the gender difference in terms of lung doses is also higher. Interestingly, for none

of the studied drugs the mean value of lung dose was significantly higher in the younger age group than in the older one. This observation may virtually be in conflict with the results of Janssens et al. (2008) who observed a decline in lung function data (especially PIF) of elderly patients. However, the mean age in their work was 76 years, while in our study it was only 65.7 (60.4 in the younger group and 71.3 in the older one). Indeed, in our recent work on the statistical analysis of the relationships between different breathing parameters of the same COPD patients (Farkas et al., 2019) we have found no significant decrease of PIF with age, which may partly explain the present results. Finally, the means of lung doses were systematically higher for the GOLD B patient group compared to the GOLD C + D group, but the differences between the means were not statistically significant at this sample size. In summary, men had higher lung deposition than women, younger patients had higher deposition than older ones and patients categorized into GOLD B group higher doses than those from GOLD C + D groups (together), but the differences were significant only for gender in case of Symbicort® and close to significant ($p = 0.08$) for the same drug upon GOLD groups. It is worth noting that splitting of Group C + D into separate C and D groups did not change the conclusions.

3.5. The perspectives of patient tailored device choice and individual specific optimization of drug delivery by numerical modelling in the light of the present results

Tables 3 and 4 demonstrate that the correlation of lung dose with native spirometric parameters is much weaker than its correlation with the breathing parameters measured through the inhalers. As

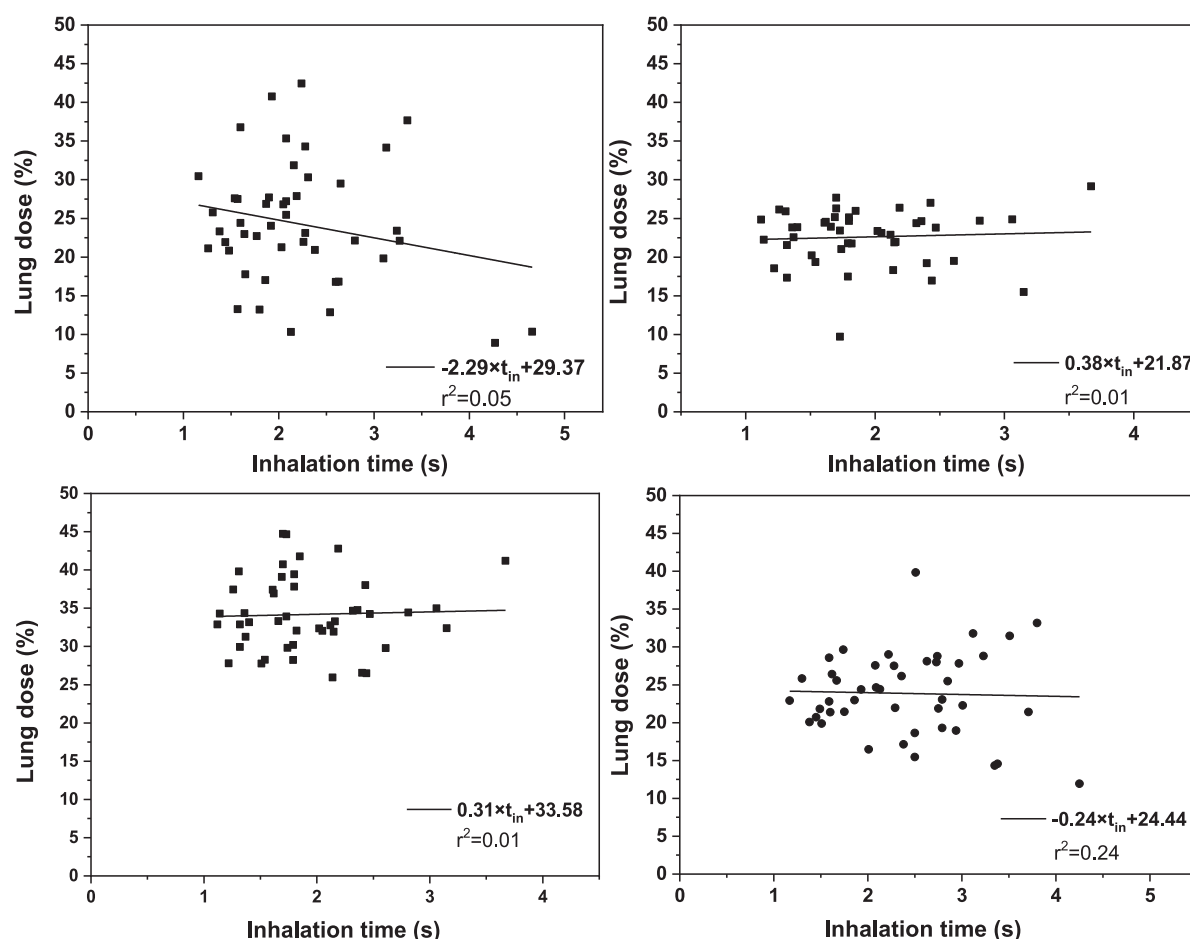


Fig. 9. Dependence of lung dose on the inhalation time (t_{in}) in case of Symbicort® Turbuhaler® (upper left panel), Onbrez® Breezhaler® (upper right panel), Seebri® Breezhaler® (lower left panel) and Bretaris® Genuair® (lower right panel). The lung dose is expressed as a percent of metered dose.

measurements through inhalers are not performed routinely, the estimation of the success of inhalation solely based on available baseline spirometric data is uncertain. In addition, Table 5 indicates that it is also not straightforward to choose the appropriate device based on the age or GOLD group the patient belongs to. For example, based on the present lung dose calculations it was possible to identify three different patients from the same disease severity group (GOLD B) who had the highest lung dose of the drug emitted by Turbuhaler®, Breezhaler® and Genuair®, respectively. This suggests that device choice and delivery optimization should be patient specific rather than based on patient groups and numerical models can be a useful tool in this context. One of the main obstacles of the use of simulations is the lack of realistic inhaler specific breathing data for each patient. This may improve in the future by the availability of connected devices automatically measuring the breathing data of the patient. Airway deposition models may provide feedback on the success of inhalation in terms of the attained lung dose based on realistic inhalation data measured by smart inhalers. Moreover, deposition based inhaler and drug choice would be possible, if smart probe inhalers with variable internal resistance were integrated with airway deposition models.

Since the present results rely on empirical fits of emitted dose and particles size fractions, the approach has its own limitations. Unfortunately, emitted dose and particle size distribution of the currently marketed drugs are not available for arbitrary inhalation flow profiles. Even the information on the value of these parameters at constant flow rates is limited in the open literature. In this work, four aerosolized drugs with relatively well documented flow rate dependency of the above characteristics were chosen. However, even for

these products it was necessary to assume fitted mathematical functions in order to tailor the emitted amount of drug and the aerodynamic properties of the emitted particles to the special inhalation characteristics of the individual patients. Moreover, the time dependent inhalation profiles of the patients were approximated with their mean values. A step towards a more precise approach would be to consider the patient-specific acceleration of the inspired flow, but as already mentioned in the methods section, this would require *in vitro* measurements of emitted dose and particle size for different flow ramp-up values. In addition, for some drugs the release of the drug is in the form of an aerosol bolus and emission takes a shorter time than the inhalation time of the patient. Improvement of the model to account for the possible puff-like drug release instead of constant emission is in progress. It is also worth noting that although the currently used aerosol deposition model has been validated against several *in vivo* and *in vitro* measured deposition datasets, it is still characterized by uncertainties due to the approximations in terms of physical models, morphological data and physiological assumptions, but also due to limited accuracy of the applied numerical schemes. All these limiting aspects should be kept in mind when interpreting the results of numerical deposition simulations of the deposition of inhalation drugs. Nevertheless, present study is an important step towards a more realistic and patient specific prediction of the deposition distribution of aerosol drugs within the human airways”

4. Conclusions

The present work has demonstrated that numerical modelling based

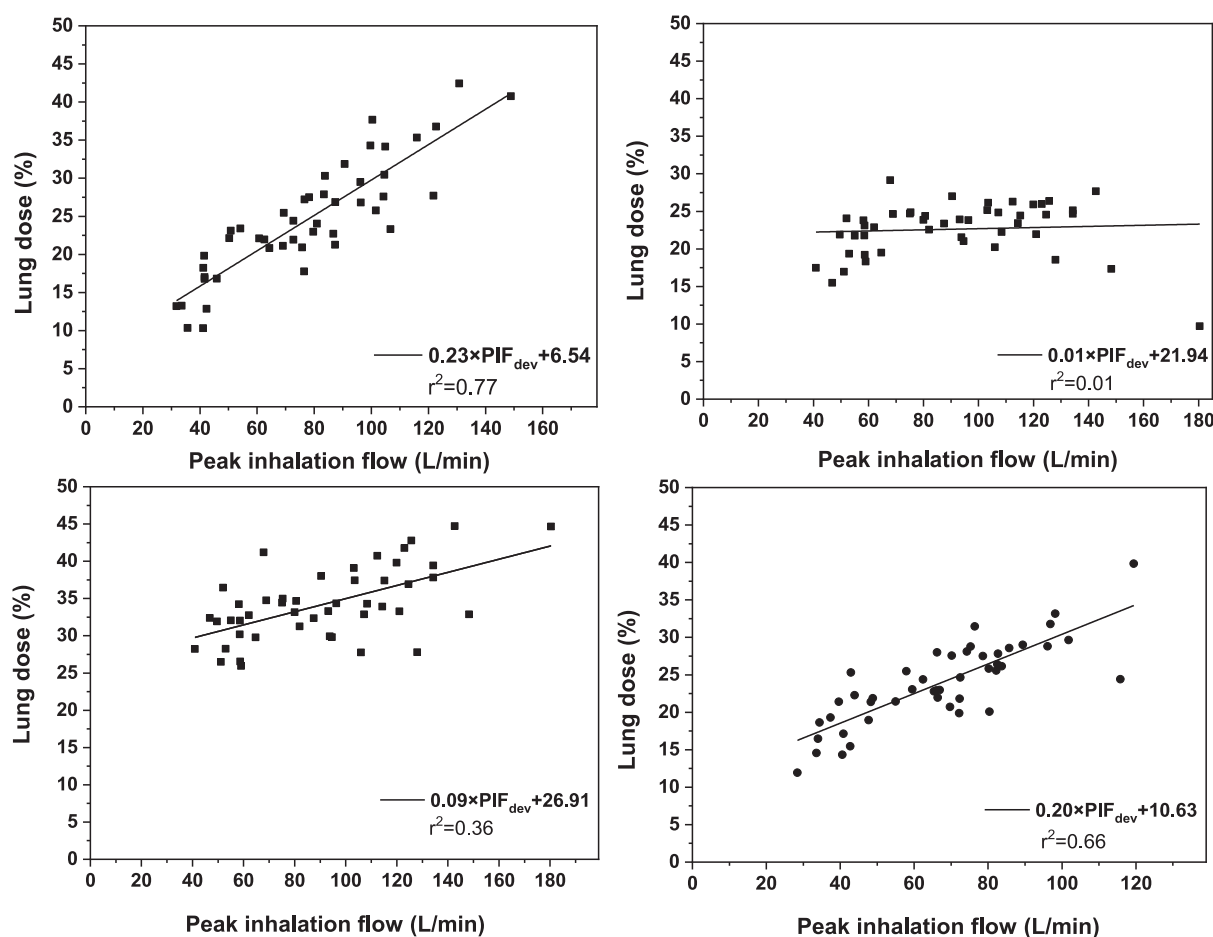


Fig. 10. Dependence of lung dose on the peak inhalation flow through the device (PIF) in case of Symbicort® Turbuhaler® (upper left panel), Onbrez® Breezhaler® (upper right panel), Seebri® Breezhaler® (lower left panel) and Bretaris® Genuair® (lower right panel). The lung dose is expressed as a percent of metered dose.

Table 3

Correlation coefficients (r) and significance (at $p = 0.05$) between the computed lung doses of Symbicort® Turbuhaler®, Onbrez® Breezhaler®, Seebri® Breezhaler® and Bretaris® Genuair® and the relevant inhalation parameters through the devices. Q – mean flow rate through the device, t_{b-h} – breath-hold time, IV – inhaled volume through the device; PIF_{dev} – peak inhalation flow through the device.

	Q (L/min)	t_{b-h} (s)	IV (L)	t_{in} (s)	PIF_{dev} (L/min)
Symbicort® Turbuhaler®	0.95 significant	0.16 not significant	0.73 significant	−0.21 not significant	0.88 significant
Onbrez® Breezhaler®	0.10 not significant	0.56 significant	0.21 not significant	0.20 not significant	0.10 not significant
Seebri® Breezhaler®	0.66 significant	0.55 significant	0.75 significant	0.10 not significant	0.60 significant
Bretaris® Genuair®	0.82 significant	0.45 significant	0.76 significant	−0.49 not significant	0.81 significant

Table 4

Correlation coefficients (and significance at $p = 0.05$) between the computed lung doses of Symbicort® Turbuhaler®, Onbrez® Breezhaler®, Seebri® Breezhaler® and Bretaris® Genuair® and the standard spirometric parameters. FEV₁ – forced expiratory volume in the first second of exhalation, FVC – forced vital capacity, PIF – peak inhalation flow, PEF – peak expiratory flow, IVC – inspiratory vital capacity, sig. – significant, not sig. – not significant.

	FEV ₁ (%)	FEV ₁ (L)	FVC (%)	FVC (L)	FEV ₁ /FVC (%)	PIF (L/min)	PEF (L/min)	IVC (L)
Symbicort® Turbuhaler®	0.38 sig.	0.55 sig.	0.27 not sig.	0.52 sig.	0.34 sig.	0.46 sig.	0.57 sig.	0.33 sig.
Onbrez® Breezhaler®	0.14 not sig.	0.16 not sig.	0.19 not sig.	0.21 not sig.	−0.08 not sig.	0.07 not sig.	0.09 not sig.	0.41 sig.
Seebri® Breezhaler®	0.35 sig.	0.54 sig.	0.35 sig.	0.58 sig.	0.10 not sig.	0.51 sig.	0.57 sig.	0.50 sig.
Bretaris® Genuair®	0.25 not sig.	0.42 sig.	0.25 not sig.	0.45 sig.	0.09 not sig.	0.49 sig.	0.52 sig.	0.32 sig.

on realistic input data can be an efficient tool of predicting the deposition distribution of aerosol drugs. The results of this study revealed that the effect of breathing parameters on the drug dose depositing in the lungs is not only patient and device specific but also drug specific, as two different drugs emitted by the same device yielded different deposition distributions. Based on the current data patients with good spirometric parameters are likely to have high lung deposition when

inhaling a drug with emitted dose and particle size sensitive to the inhalation flow rate (e.g. Symbicort® Turbuhaler®). Conversely, patients with lower lung capacity show better deposition results when inhaling drugs emitting a more constant amount of drug and particles with more stable aerodynamic characteristics. Powerful inhalation and long breath-hold generally indicated in the patient information leaflet, but while the first can improve the lung deposition mostly in case of

Table 5

Mean values and standard deviations of different COPD populations grouped upon gender, age and disease class.

	Gender women	men	Age ≤65 years	>65 years	Disease group GOLD B	GOLD C + D
Symbicort® Turbuhaler®	26.7 (± 8.3) significant	20.5 (± 5.3) not significant	24.7 (± 8.7) not significant	23.6 (± 6.9)	26.0 (± 7.9)	22.0 (± 7.4)
Onbrez® Breezhaler®	22.7 (± 4.2) not significant	22.5 (± 2.7) not significant	22.4 (± 3.2) not significant	22.9 (± 4.0)	23.0 (± 3.9)	22.1 (± 3.1)
Seebri® Breezhaler®	35.7 (± 5.1) significant	32.0 (± 3.4) not significant	34.4 (± 5.7) not significant	34.0 (± 3.7)	35.3 (± 4.8)	32.9 (± 4.6)
Bretaris® Genuair®	24.9 (± 6.1) not significant	22.3 (± 4.0) not significant	24.0 (± 6.6) not significant	23.8 (± 3.9)	24.9 (± 5.6)	22.6 (± 5.1)

Symbicort® Turbuhaler®, the second leads to high deposition in case of drugs emitted by Breezhaler® and Genuair®. Present results demonstrate that for an effective therapy a more personalized drug and device choice and breathing optimization would be necessary in the future. Carefully validated numerical models can be a powerful tool in this context.

Author statement

AH participated in conceptualization, development of methodology, interpretation of the results, editing and review of the manuscript. ÁF performed the numerical simulations and took part in data analysis and manuscript writing. ASz took part in the conceptualization, development of methodology, preparation of input data and review of the manuscript. GT participated in conceptualization, development of methodology, interpretation of the results, editing and review of the manuscript. ZsSz took part in the conceptualization, development of methodology, preparation of input data and review of the manuscript. GG had substantial contribution to the conceptualization of the work, investigation of input data, interpretation of the results and review of the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2020.105508.

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